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MINI-REVIEW *Developments in reproductive biology and medicine*

Effects of COVID-19 and mRNA vaccines on human fertility

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ABSTRACT: The coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has precipitated a global health crisis of unprecedented proportions. Because of its severe impact, multiple COVID-19 vaccines are being rapidly developed, approved and manufactured. Among them, mRNA vaccines are considered as ideal candidates with special advantages to meet this challenge. However, some serious adverse events have been reported after their application, significantly increasing concerns about the safety and efficacy of the vaccines and doubts about the necessity of vaccination. Although several fertility societies have announced that COVID-19 mRNA vaccines are unlikely to affect fertility, there is no denying that the current evidence is very limited, which is one of the reasons for vaccine hesitancy in the population, especially in pregnant women. Herein, we provide an in-depth discussion on the involvement of the male and female reproductive systems during SARS-CoV-2 infection or after vaccination. On one hand, despite the low risk of infection in the male reproductive system or fetus, COVID-19 could pose an enormous threat to human reproductive health. On the other hand, our review indicates that both men and women, especially pregnant women, have no fertility problems or increased adverse pregnancy outcomes after vaccination, and, in particular, the benefits of maternal antibodies transferred through the placenta outweigh any known or potential risks. Thus, in the case of the rapid spread of COVID-19, although further research is still required, especially a larger population-based longitudinal study, it is obviously a wise option to be vaccinated instead of suffering from serious adverse symptoms of virus infection.

Key words: COVID-19 / coronavirus disease 2019 / SARS-CoV-2 / severe acute respiratory syndrome coronavirus 2 / mRNA vaccine / reproductive system / pregnant women / fertility / ACE2 / angiotensin-converting enzyme 2

Introduction

The link between viral infection and infertility has been studied for decades. Numerous viruses, including Zika virus, HIV and cytomegalovirus have been detected in human semen, among which some can affect male fertility potential (Mate *et al.*, 2015; Counotte *et al.*, 2018). Moreover, because of the contribution of the immune privilege of the testes and the resistance of blood–testis barrier (BTB) to antiviral drugs, several viruses can persist in semen and last longer than in other body fluids (Liu *et al.*, 2018; Paz-Bailey *et al.*, 2019). Undoubtedly, there is an urgent need for a thorough exploration of the effect of coronavirus disease 2019 (COVID-19) on the human reproductive system. Meanwhile, given the potential damage of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to the reproductive system, some individuals suspect that the vaccine which mimics the virus (mRNA vaccine) may also affect fertility via the same mechanism. Notably, although more than 4 billion vaccine doses have been currently administered, pregnant women are always excluded from the initial clinical trials of mRNA vaccination. However, as of 30 August 2021, the US Centers for Disease Control and Prevention (CDC) had reported more than 155 000 participants who were pregnant at the time they received vaccination, which draws attention to the safety of mRNA vaccines while pregnant. Previous studies have revealed that the type I viral envelope protein and human syncytin-1 protein involved in the formation of the placenta share analogous structural features, especially in the regions of N- and C-terminal heptad repeats (Gong *et al.*, 2005). Some skeptics and anti-vaccination movements have claimed that vaccine mRNA-translated antibodies (Abs) against the spike protein (S protein) may cross-react with syncytin-1, leading to adverse pregnancy outcomes. Therefore, there is a significant and urgent need to review the limited data and theoretical considerations for informing clinical guidelines and our understanding regarding the various effects of COVID-19 and vaccines on the human reproductive system.

Effects of COVID-19 on male and female reproductive systems

It is well-known that the BTB protects spermatogenic cells from various pathogens, but the inflammatory state caused by COVID-19 might change this situation, as high levels of interleukin-6 can disrupt the integrity of the BTB and further facilitate virus infiltration. Moreover, the testis is one of the tissues with the highest expression of angiotensin-converting enzyme 2 (ACE2) mRNA and protein. Thus, in the early stage of this epidemic, some people predicted that the testis might be susceptible to SARS-CoV-2. Indeed, one or several cofactors, such as transmembrane serine protease 2 (TMPRSS2), transmembrane serine protease 4 (TMPRSS4), cathepsin B (CTSB) and cathepsin L (CTSL), which can cleave the S protein, are also very pivotal for virus entry. Based on the fact that a few spermatogonia are the only cells expressing ACE2 and TMPRSS2 in the testis (Stanley *et al.*, 2020), some people suggested that the testis is unlikely to be a target for SARS-CoV-2. In the meantime, other individuals argued that the high co-expression of ACE2 and CTSL in testis might increase testicular susceptibility to infection (Kerslake *et al.*, 2020). Hence, whether SARS-CoV-2 can infect the male reproductive system remains controversial.

Table I summarizes the clinical characteristics and the detection results of SARS-CoV-2 in semen or testicular tissue among infected and recovered subjects included in the current studies (Holtmann *et al.*, 2020; Kayaaslan *et al.*, 2020; Li *et al.*, 2020; Pan *et al.*, 2020; Song *et al.*, 2020; Yang *et al.*, 2020; Gacci *et al.*, 2021; Guo *et al.*, 2021; Ma *et al.*, 2021; Ruan *et al.*, 2021). In 210 patients who achieved clinical recovery, the positive rate of semen testing was only 1.4%, which was lower than 6.9% in 58 patients who were in the acute stage of infection. This result is understandable because the virus gradually clears up as patients recover. Furthermore, it is noteworthy that the time from disease onset or clinical recovery to semen sample collection was mostly short (range 2–11 days) in patients with positive semen, except for one patient who tested positive 21 days after recovery. In addition, although all SARS-CoV-2 target genes were detected in the semen of this patient and he had unprotected oral, vaginal and anal sex with a stable partner after recovering from COVID-19, the retest results of the pharyngeal, vaginal and rectal swabs from his partner were all negative (Gacci *et al.*, 2021), indicating that it was viral RNA instead of live virus detected in the patient. In terms of testicular tissue testing, the available experimental data are limited. Among tissue samples obtained from 13 deceased patients with COVID-19, SARS-CoV-2 was detected in only one case that had a high viral load. In addition to testis, the lung, kidney and spleen of this patient were also positive. Moreover, the authors mentioned that the testicular tissue sampled contained fibrovascular tissue (Li *et al.*, 2020). Thus, it is probable that the detected virus was present in blood rather than in testicular tissue. Similarly, for the positive result in semen, the probability of viral contamination from non-semen sources could not be completely ruled out. On one hand, most semen samples were collected by masturbation, and the virus on the epidermis was likely to cause contamination. On the other hand, droplets and aerosols are the two main transmission routes of SARS-CoV-2. Failure to use aerosol-tight caps of the centrifuge bucket or incomplete closure of the lids during sample collection and centrifugation may result in contamination of the sample from the external environment. In addition, detecting the N2 target gene alone was considered to have the potential to produce false-positive results (Vogels *et al.*, 2020). In general, shedding of SARS-CoV-2 into the semen or testis is a rare event, and even if it occurs, the virus cannot exist for a long period. Nevertheless, taking into consideration the fact that many patients have shown different proportions of reproductive system symptoms, such as scrotal discomfort (17.6%, 6/34), seminiferous tubular injury (100.0%, 11/11), low sperm motility (33.3%, 4/12) and oligo-cryptoazoospermia (25.5%, 11/43) (Table I), even a minor risk is not negligible. Moreover, almost every proportion is higher than the virus-positive rate mentioned above. Thus, it is reasonable to speculate that these abnormalities are caused by other reasons, for instance hyperthermia and hypoxia lead to vascular disturbances and organ-related oxidative stress, thereby triggering the inflammation in the testicular tissue. In addition to the damage to the testes, abnormal hormone levels were also found in male patients, such as high LH and low testosterone levels (Ma *et al.*, 2020), and more seriously, in men with COVID-19, lower testosterone concentrations and increased estradiol-to-testosterone ratios have been proven to be associated with disease severity, inflammation and mortality (Dhindsa *et al.*, 2021).

In previous papers, we speculated that SARS-CoV-2 may infect the ovary, uterus and vagina through the extensive expression of ACE2, thereby disturbing the female reproductive functions and leading to infertility and menstrual disorder (Jing *et al.*, 2020). Nevertheless, some studies did not observe the co-expression of ACE2 with TMPRSS2 because of the low concentration of TMPRSS2 in human myometrium, ovaries, fallopian tube and breast (Nguyen *et al.*, 2018; Goad *et al.*, 2020). Indeed, in the absence of TMPRSS2, the virus can also achieve cell entry via an endosomal pathway in which CTSL plays an important role (Kawase *et al.*, 2012). Moreover, endometrium gene expression is affected by the menstrual cycle. For example, Henarejos-Castillo *et al.* (2020) found that the expression levels of proteases, such as TMPRSS2, TMPRSS4, CTSB and CTSL, significantly increased from the early secretory to mid-secretory (Henarejos-Castillo *et al.*, 2020). These findings further enhance the potential of infection in the female reproductive system. Consistent with this, three studies have reported the presence of SARS-CoV-2 in vaginal swabs (Scorzolini *et al.*, 2020; Barber *et al.*, 2021; Schwartz *et al.*, 2021). However, the overall side effects of COVID-19 on the female reproductive system have remained unclear. We know only that some patients have exhibited a decrease in menstrual volume or cycle prolongation (Li *et al.*, 2021), which may indicate changes in sex hormones caused by ovarian suppression. In addition, given that existing studies are limited by their small sample size and brief duration, further studies and follow-up are urgently needed to assess the long-term effects of COVID-19.

SARS-CoV-2 infection in pregnant women and vertical transmission

Given the immunosuppressive state and physiological adaptive changes that occur during pregnancy (increased oxygen consumption, diaphragm elevation caused by the gravid uterus, decreased total lung volume, edema of respiratory tract mucosa, etc.), pregnant women are

Table I SARS-CoV-2 positive rate in semen or testicular tissue and clinical characteristics among patients with COVID-19.

Study design	Sample	Infection stage		Recovery stage		Reproductive system symptom	Reference
		Positive rate	Time from a positive swab test or disease onset to sample collection	Positive rate	Time from clinical recovery to sample collection		
Cohort study	Semen	26.7% (4/15)	4 patients with positive test results: range 6–11 days Others: not provided	8.7% (2/23)	2 patients with positive test results: 2 and 3 days, respectively Others: not provided	–	Li *et al.*, 2020
Pilot cohort study	Semen	0 (0/2)	Not provided	0 (0/18)	Range 8–54 days	Impaired sperm quality (4/18), testicular discomfort (1/18)	Holtmann *et al.*, 2020
Cohort study	Semen	0 (0/12)	All the 23 subjects: median 32 days	0 (0/11)	All the 23 subjects: median 32 days	–	Guo *et al.*, 2021
Cohort study	Semen	0 (0/16)	Range 0–7 days, median 1 day	–	–	–	Kayaaslan *et al.*, 2020
Cohort study	Semen	0 (0/12)	Range 5–109 days	–	–	Low sperm motility (4/12)	Ma *et al.*, 2021
Descriptive study	Semen	0 (0/1)	40 days	0 (0/11)	Range 14–42 days	–	Song *et al.*, 2020
Observational, cross-sectional study	Semen	–	–	0 (0/34)	Not provided	Scrotal discomfort (6/34)	Pan *et al.*, 2020
Prospective cross-sectional study	Semen	–	–	2.3% (1/43)	1 patient with positive test results: 21 days Others: range 13–67 days	Oligo-crypto-azoospermia (11/43)	Gacci *et al.*, 2021
Case-controlled study	Semen	–	–	0 (0/70)	Range 64–93 days, median 80 days	Decreased sperm concentration	Ruan *et al.*, 2021
Total	Semen	6.9% (4/58)		1.4% (3/210)			
Cohort study	Testicular tissue	8.3% (1/12)	Range 20–75 days	–	–	Seminiferous tubular injury (11/11)	Yang *et al.*, 2020
Descriptive study	Testicular tissue	0 (0/1)	41 days	–	–	–	Song *et al.*, 2020
Total	Testicular tissue	7.7% (1/13)		–			

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

thought to be more susceptible to COVID-19 infection and more intolerant to hypoxia than the general population. However, initial data have not consistently shown that pregnant patients are at higher risk of severe disease. Liu *et al.* (2020) reported that the frequency of intensive care unit (ICU) admission or mechanical ventilation was similar between 21 pregnant women and 19 age-matched non-pregnant controls (Liu *et al.*, 2020). Such a result may be attributed, at least in part, to the limitations of small samples and short follow-up terms, as subsequent data from four large hospitals in France and Belgium suggested that gravidas with COVID-19 had significantly more events of hospitalization (58.2% versus 17.4%) and invasive ventilation (10.2% versus 1.7%) (Badr *et al.*, 2020) than controls. Similarly, in studies of 400 000 women in the USA between 15 and 44 years of age with symptomatic COVID-19, pregnant individuals were more likely to experience ICU admission, intubation and death (Zambrano *et al.*, 2020). Apart from this, the endothelium in the placental decidua and

chorionic villi presents an altered state, exhibiting thrombosis, infarcts and remodeling of vascular walls. This indicates fetal and maternal vascular malperfusion, which may be associated with oligohydramnios, fetal growth restriction, preterm birth and stillbirth reported by some studies (Breslin et al., 2020; Chen et al., 2020; Knight et al., 2020; Pereira et al., 2020; Wu et al., 2020; Yan et al., 2020; Al-Matary et al., 2021; Damar Çakırca et al., 2021; Keita et al., 2021; Nayak et al., 2021; Sahin et al., 2021) (Table II). Compared with noninfected pregnancies, the rates of cesarean delivery are higher in pregnancies with SARS-CoV-2 infection, especially in China (approaching 90%). Obviously, in addition to other obstetric indications, concerns about the effects of COVID-19 on pregnancy are also responsible for this phenomenon (Table II).

Of note, expression of various receptor-protease combinations, including ACE2 + TMPRSS2, ACE2 + FURIN, basignin (BSG) + TMPRSS2, BSG + FURIN, dipeptidyl peptidase-4 (DPP4) + TMPRSS2 and DPP4 + FURIN, was evident in cytotrophoblasts and syncytiotrophoblasts (Singh et al., 2020). Moreover, SARS-CoV-2 RNA can indeed be detected in placental or membrane swabs from women infected with COVID-19 (Penfield et al., 2020). Thus, some studies have highlighted a very strong possibility of vertical transmission (Kulkarni et al., 2021). However, the literature to date on intrauterine infection with SARS-CoV-2 is highly speculative, and the conclusion is still unclear. One study reported that among 212 samples, including 155 throat swabs, 19 feces, 19 urine and 19 gastric juice samples from 132 neonates, all were negative for SARS-CoV-2 (Juan et al., 2020). However, elevated IgM Abs in blood drawn from the neonates after birth were identified at two hospitals in Wuhan, China (Dong et al., 2020; Zeng et al., 2020). Considering that IgM cannot cross the placenta owing to its large molecular structure, it seems reasonable to assume that it is produced by the newborn following *in utero* infection. However, IgM assay is a challenging way to diagnose many congenital infections because of its susceptibility to false-positive or false-negative results, cross-reactivity, and additional testing challenges. For example, in congenital rubella syndrome, IgM testing can yield false-positive results that are attributed to incomplete removal of IgG or the presence of rheumatoid factor (Cradock-Watson et al., 1980). Most importantly, in the past year, few cases have been reported of neonatal infection potentially acquired *in utero*. Thus, most data indicate that the risk of maternal-fetal transmission might be low at present.

Impact of mRNA vaccination on human fertility

The current evidence of the impact of COVID-19 mRNA vaccine on human fertility is still very limited. Fortunately, two studies have shown that both BNT162b2 and mRNA-1273 vaccination have no influence on sperm parameters, including sperm concentration, semen volume, sperm motility, sperm volume and total number of motile sperm (Gonzalez et al., 2021; Safrai et al., 2021). Similarly, an assessment of follicular steroidogenesis and oocyte quality did not show any measurable difference when compared with unvaccinated women (Bentov et al., 2021). Moreover, Orvieto et al. (2021) reported that many IVF treatment parameters, such as the number of oocytes and mature oocytes retrieved, fertilization rate and the ratio of top-quality embryos (TQEs) per fertilized oocyte, did not significantly differ between the pre- and post-BNT162b2 vaccination groups (Orvieto et al., 2021): these researchers had also found that COVID-19 infection could lead to a significantly lower proportion of TQEs (Orvieto et al., 2021). Overall, these primary findings unanimously indicate that vaccination will not result in any measurable detrimental effect on the female or male reproductive system.

Impact of mRNA vaccination on pregnant women and fetuses

Despite the serious threat of COVID-19 to pregnant women, concerns about the safety and efficacy of mRNA vaccines have still delayed most vaccinations in this group. As mentioned above, the SARS-CoV-2 S protein is assumed to be similar to the human syncytin-1 protein. However, the similarities are very limited, as when the search was limited to the small stretches of similarity, only two identical two-amino-acid stretches were found (Kloc et al., 2021). In reality, a comparably low degree of similarity can be found between the S protein and any other protein in the human body. Furthermore, short contiguous amino acid matches alone are a poor predictor of allergenic cross-reactivity. If the protein pairs share <35% identity over 80 amino acids, they are not cross-reactive even with eight-amino-acid contiguous matches (Herman et al., 2009). Consistent with this, Lu-Culligan and Iwasaki (2021) analyzed serum from women with COVID-19 and did not detect any reactivity of syncytin-1 protein to the patients' Abs (Lu-Culligan and Iwasaki, 2021) and, most importantly, several recent studies have demonstrated no difference in implantation or sustained implantation rates (transvaginal ultrasound-documented positive fetal heart tones at two time points at least 1 week apart) between the general population and women previously vaccinated with BNT162b2 or mRNA-1273 (Aharon et al., 2021; Morris, 2021; Morris et al., 2021).

Of note, both of the COVID-19 mRNA vaccines (mRNA-1273 and BNT162b2) that have been granted emergency use authorization could induce Th1 immunity and trigger interferon-γ + CD8 + T-cell responses in men and in non-pregnant women. Given that favorable obstetric outcomes depend a great deal on an adequate balance of Th1/Th2 immunity (Saito et al., 2010), these results raised concerns about whether the effect of the vaccine on the cellular immune system would present a risk to pregnancy. However, several studies have reported similarly low incidences of pregnancy complications and adverse obstetric outcomes, such as miscarriage and preterm birth, in vaccinated gravidas and the general population (Bookstein Peretz et al., 2021; Shimabukuro et al., 2021). As shown in Table II, vaccinated mothers had a significantly lower risk of premature rupture of membranes (0.8% versus 8.3%), stillbirth (0.1% versus 1.0%) and preterm delivery (7.3% versus 21.4%) when compared with those infected with COVID-19. No differences were found between the vaccinated and unvaccinated groups in newborn complications (such as newborn respiratory complications) (Wainstock et al., 2021). We also noticed an abnormal miscarriage rate (4.1%) in COVID-19 patients (Table II). This may be partially attributed to the higher probability of receiving special care and attention when they were diagnosed as COVID-19 positive. Moreover, it must be noted that the risks of COVID-19 to gravidas might be underestimated in the current studies for the

Table II Maternofetal outcomes of women with COVID-19 or after COVID-19 mRNA vaccination.

Subjects' characteristic	Geographic area of focus	Pregnancy	Infection or vaccination in the third trimester	PROM	Pregnancy completed	Obstetric outcomes			Mode of delivery			Reference
						Pregnancy loss	Stillbirth	Preterm delivery	Vaginal	CS	COVID-19 as main CS indication	
COVID-19 infection	USA	43	Median 37 weeks	NP	18	NP	NP	5.6% (1/18)	55.6% (10/18)	44.4% (8/18)	0/8	Breslin *et al.*, 2020
	UK	427	80.1% (342/427)	NP	266	1.5% (4/266)	1.1% (3/266)	24.8% (66/266)	40.5% (106/262)	59.5% (156/262)	26.9% (42/156)	Knight *et al.*, 2020
	Spain	60	56.7% (34/60)	NP	23	NP	NP	8.7% (2/23)	78.3% (18/23)	21.7% (5/23)	20.0% (1/5)	Pereira *et al.*, 2020
	France	126	62.7% (79/126)	NP	126	NP	0/126	42.1% (53/126)	48.4% (61/126)	51.6% (65/126)	35.4% (23/65)	Keita *et al.*, 2021
	Turkey	533	44.7% (238/533)	NP	144	8.3% (12/144)	0.7% (1/144)	15.3% (22/144)	33.6% (44/131)	66.4% (87/131)	NP	Sahin *et al.*, 2021
	Saudi Arabia	288	Median 38 weeks	5.6% (16/288)	204	0/204	2.0% (4/204)	15.2% (31/204)	64.2% (131/204)	35.8% (73/204)	NP	Al-Matary *et al.*, 2021
	India	162	NP	15.4% (25/162)	162	NP	1.2% (2/162)	16.7% (27/162)	36.4% (59/162)	63.6% (103/162)	NP	Nayak *et al.*, 2021
	Turkey	75	57.3% (43/75)	NP	41	14.6% (6/41)	2.4% (1/41)	26.8% (11/41)	42.9% (15/35)	57.1% (20/35)	NP	Damar Cakirca *et al.*, 2021
	China	116	91.4% (106/116)	5.2% (6/116)	100	1.0% (1/100)	0/100	21.0% (21/100)	14.1% (14/99)	85.9% (85/99)	38.8% (33/85)	Yan *et al.*, 2020
	China	23	87.0% (20/23)	8.7% (2/23)	23	13.0% (3/23)	NP	NP	10.0% (2/20)	90.0% (18/20)	NP	Wu *et al.*, 2020
	China	118	63.6% (75/118)	NP	77	11.7% (9/77)	0/77	18.2% (14/77)	7.4% (5/68)	92.6% (63/68)	60.3% (38/63)	Chen *et al.*, 2020
	Total	1971	63.4% (937/1478)	8.3% (49/589)	1184	4.1% (35/855)	1.0% (11/1120)	21.4% (248/1161)	40.5% (465/1148)	59.5% (683/1148)	35.9% (137/382)	
Receive mRNA vaccination	Israel	390	31.0% (121/390)	0.8% (3/390)	57	0/57	0/57	0/57	82.5% (47/57)	17.5% (10/57)	NP	Bookstein Peretz *et al.*, 2021
	CDC v-safe* pregnancy registry	3958	25.7% (1019/3958)	NP	827	13.8% (114/827)	0.1% (1/827)	7.3% (60/827)	NP	NP	NP	Shimabukuro *et al.*, 2021

CDC, Centers for Disease Control and Prevention; CS, cesarean section; NP, not provided; PROM, premature rupture of membranes.
*v-safe is a new CDC smartphone-based active-surveillance system developed for the COVID-19 vaccination programme; enrollment is voluntary.

following reasons: first, the infection was mild or even asymptomatic in the majority of cases included, and second, more than 63% of patients included were in the third trimester of pregnancy (Table II), but it is known that approximately 80% of pregnancy losses occur within the first trimester.

The effects and benefits of mRNA vaccines on pregnant women are undisputed. After 14 days, the incidence of documented SARS-CoV-2 infection in BNT162b2-vaccinated pregnant women group began to decrease dramatically compared with unvaccinated pregnant controls (Dagan et al., 2021). Moreover, maternal Abs, whether produced after infection or vaccination, could protect newborns against infection, and further reduce the hesitation of pregnant women to be vaccinated. Previous studies have reported that the transfer of SARS-CoV-2-specific Abs to the fetus is significantly impaired among patients infected during the third trimester (Edlow et al., 2020; Atyeo et al., 2021; Beharier et al., 2021). Fortunately, this deficiency is not observed in second-trimester infection. At the time of delivery, maternal and cord blood S-specific Abs as well as the transfer ratio were high in individuals who had recovered from COVID-19 several months previously (Beharier et al., 2021). This phenomenon of the lag in S-specific Abs transfer across the placenta can be used to explain the different transfer ratios measured in pregnant women who received the BNT162b2 mRNA COVID-19 vaccines in various studies (Beharier et al., 2021; Rottenstreich et al., 2021). A higher transfer ratio was associated with an increasing duration between the onset of maternal vaccination and time of delivery. Given that maternal IgG can cross the placenta barrier and approach maternal titers in the fetus within 15 days following the first dose of BNT162b2 mRNA vaccine (Beharier et al., 2021), and the maternal Ab transfer through the placenta begins from the 17th to 18th week of pregnancy and peaks as gestation progresses, maternal vaccination starting in the early second trimester of gestation might be optimal for newborn acquisition of innate immunity against SARS-CoV-2 infection. Ideally, to optimize protection for both the mother and her infant, it is best to vaccinate within the critical time window. Nevertheless, it is worth mentioning that when compared with prior studies of vaccine-elicited Abs to pertussis, influenza, rubella and hepatitis B, neonatal Ab levels were satisfactory, although the placental transfer ratios were relatively lower in women who were vaccinated during the third trimester (Rottenstreich et al., 2021). In addition, considering that protection from breast milk Abs is less effective than from transplacental Abs in infants, it is prudent to say that pregnant women in the third trimester should also receive the COVID-19 vaccine, in particular those who live in areas of high transmission and those who are frontline health workers.

Conclusion

COVID-19 poses a threat to the reproductive systems of both males and females. The presence of SARS-CoV-2 in the vagina and placenta underlies the impairment of female fertility. However, although the virus has also been detected in semen or testicular tissues, whether it can infect the male reproductive system remains controversial because of the extremely low positive detection rate and the probability of contamination from non-semen sources during the testing process. Moreover, even if this infection occurs, the virus cannot exist for a long period. Thus, the various reproductive system symptoms exhibited by many male patients may be attributed to other causes, such as hyperthermia and hypoxia. It is worth mentioning that given the association between lower testosterone concentrations and disease severity and mortality in men with COVID-19, further research is urgently needed to clarify whether testosterone could be used for risk stratification and whether testosterone supplementation or even augmentation could improve clinical outcomes. In addition, gravidas have an increased risk of severe COVID-19 when compared with non-pregnant women of similar age, and adverse maternal and obstetric outcomes are more prone to occur among pregnant women with COVID-19 than among uninfected gravidas. Fortunately, current evidence still supports the low risk of maternal–fetal transmission, but it remains necessary to systematically screen for any suspected SARS-CoV-2 infection during pregnancy, provide high-quality care before, during and after childbirth, and conduct long-term follow-up of confirmed mothers and their newborns.

Recent guidelines from the CDC recommend obtaining COVID-19 mRNA vaccination for all individuals 12 years and older, including those who are pregnant, breastfeeding, or trying to get pregnant, and the World Health Organization's Strategic Advisory Group of Experts has reached a similar conclusion. Nevertheless, anti-vaccination advocates still hold that there are not enough data to justify the safety and effectiveness of vaccines, and large-scale vaccination may result in some unprecedented issues. Admittedly, data on COVID-19 mRNA vaccines are incomplete when compared with traditional vaccines based on long-term studies with large samples. However, accumulating evidence has indicated that serious adverse events caused by mRNA vaccines are very rare and women or men do not experience fertility problems after vaccination. In terms of pregnant women, the benefits of vaccination outweigh any known or potential risks although the durability of maternally derived neonatal Abs to further maintain neonatal immunity is an unsolved issue. Most importantly, given the rapid and extensive spread of COVID-19, the potential side effects of vaccination on human health should be compared with adverse COVID-19 outcomes rather than being considered alone. Based on our review, from the perspective of reproduction, it is obviously a wise option to be vaccinated instead of suffering from serious adverse symptoms of SARS-CoV-2 infection. In addition, in view of the emergence of vaccine breakthrough infections, individuals, especially pregnant women, should strictly follow infection control guidelines even if vaccinated.

Data availability

Data sharing is not applicable to this article as no new datasets (human or animal) were generated or analyzed during the current study.

Authors' roles

All authors contributed to the literature review for the manuscript. The first draft of the manuscript was written by F.C. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the

work as a whole, and have given their approval for this version to be published.

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Conflict of interest

The authors declare that there are no conflicts of interest in connection with this article.

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